



Year: 2018

Clinical, Radiologic, Pathologic, and Molecular Characteristics of Long-Term Survivors of Diffuse Intrinsic Pontine Glioma (DIPG): A Collaborative Report From the International and European Society for Pediatric Oncology DIPG Registries

Hoffman, Lindsey M ; Veldhuijzen van Zanten, Sophie E M ; Colditz, Niclas ; Baugh, Joshua ; Chaney, Brooklyn ; Hoffmann, Marion ; Lane, Adam ; Fuller, Christine ; Miles, Lili ; Hawkins, Cynthia ; Bartels, Ute ; Bouffet, Eric ; Goldman, Stewart ; Leary, Sarah ; Foreman, Nicholas K ; Packer, Roger ; Warren, Katherine E ; Broniscer, Alberto ; Kieran, Mark W ; Minturn, Jane ; Comito, Melanie ; Broxson, Emmett ; Shih, Chie-Schin ; Khatua, Soumen ; Chintagumpala, Murali ; Carret, Anne Sophie ; Escorza, Nancy Yanez ; Hassall, Timothy ; Ziegler, David S ; Gottardo, Nicholas ; et al ; Grotzer, M A ; Gerber, N U

Abstract: Purpose Diffuse intrinsic pontine glioma (DIPG) is a brainstem malignancy with a median survival of < 1 year. The International and European Society for Pediatric Oncology DIPG Registries collaborated to compare clinical, radiologic, and histomolecular characteristics between short-term survivors (STSs) and long-term survivors (LTSs). Materials and Methods Data abstracted from registry databases included patients from North America, Australia, Germany, Austria, Switzerland, the Netherlands, Italy, France, the United Kingdom, and Croatia. Results Among 1,130 pediatric and young adults with radiographically confirmed DIPG, 122 (11%) were excluded. Of the 1,008 remaining patients, 101 (10%) were LTSs (survival ≥ 2 years). Median survival time was 11 months (interquartile range, 7.5 to 16 months), and 1-, 2-, 3-, 4-, and 5-year survival rates were 42.3% (95% CI, 38.1% to 44.1%), 9.6% (95% CI, 7.8% to 11.3%), 4.3% (95% CI, 3.2% to 5.8%), 3.2% (95% CI, 2.4% to 4.6%), and 2.2% (95% CI, 1.4% to 3.4%), respectively. LTSs, compared with STSs, more commonly presented at age < 3 or > 10 years (11% v 3% and 33% v 23%, respectively; $P < .001$) and with longer symptom duration ($P < .001$). STSs, compared with LTSs, more commonly presented with cranial nerve palsy (83% v 73%, respectively; $P = .008$), ring enhancement (38% v 23%, respectively; $P = .007$), necrosis (42% v 26%, respectively; $P = .009$), and extrapontine extension (92% v 86%, respectively; $P = .04$). LTSs more commonly received systemic therapy at diagnosis (88% v 75% for STSs; $P = .005$). Biopsies and autopsies were performed in 299 patients (30%) and 77 patients (10%), respectively; 181 tumors (48%) were molecularly characterized. LTSs were more likely to harbor a HIST1H3B mutation (odds ratio, 1.28; 95% CI, 1.1 to 1.5; $P = .002$). Conclusion We report clinical, radiologic, and molecular factors that correlate with survival in children and young adults with DIPG, which are important for risk stratification in future clinical trials.

DOI: <https://doi.org/10.1200/JCO.2017.75.9308>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-162631>

Journal Article

Published Version

Originally published at:

Hoffman, Lindsey M; Veldhuijzen van Zanten, Sophie E M; Colditz, Niclas; Baugh, Joshua; Chaney, Brooklyn; Hoffmann, Marion; Lane, Adam; Fuller, Christine; Miles, Lili; Hawkins, Cynthia; Bartels, Ute; Bouffet, Eric; Goldman, Stewart; Leary, Sarah; Foreman, Nicholas K; Packer, Roger; Warren, Katherine E; Broniscer, Alberto; Kieran, Mark W; Minturn, Jane; Comito, Melanie; Broxson, Emmett; Shih, Chie-Schin; Khatua, Soumen; Chintagumpala, Murali; Carret, Anne Sophie; Escorza, Nancy Yanez; Hassall, Timothy; Ziegler, David S; Gottardo, Nicholas; et al; Grotzer, M A; Gerber, N U (2018). Clinical, Radiologic, Pathologic, and Molecular Characteristics of Long-Term Survivors of Diffuse Intrinsic Pontine Glioma (DIPG): A Collaborative Report From the International and European Society for Pediatric Oncology DIPG Registries. *Journal of Clinical Oncology*, 36(19):1963-1972.
DOI: <https://doi.org/10.1200/JCO.2017.75.9308>

Clinical, Radiologic, Pathologic, and Molecular Characteristics of Long-Term Survivors of Diffuse Intrinsic Pontine Glioma (DIPG): A Collaborative Report From the International and European Society for Pediatric Oncology DIPG Registries

Lindsey M. Hoffman, Sophie E.M. Veldhuijzen van Zanten, Niclas Colditz, Joshua Baugh, Brooklyn Chaney, Marion Hoffmann, Adam Lane, Christine Fuller, Lili Miles, Cynthia Hawkins, Ute Bartels, Eric Bouffet, Stewart Goldman, Sarah Leary, Nicholas K. Foreman, Roger Packer, Katherine E. Warren, Alberto Broniscer, Mark W. Kieran, Jane Minturn, Melanie Comito, Emmett Broxson, Chie-Schin Shih, Soumen Khatua, Murali Chintagumpala, Anne Sophie Carret, Nancy Yanez Escorza, Timothy Hassall, David S. Ziegler, Nicholas Gottardo, Hetal Dholaria, Renee Doughman, Martin Benesch, Rachid Drissi, Javad Nazarian, Nada Jabado, Nathalie Boddaert, Pascale Varlet, Géraldine Giraud, David Castel, Stephanie Puget, Chris Jones, Esther Hulleman, Piergiorgio Modena, Marzia Giagnacovo, Manila Antonelli, Torsten Pietsch, Gerrit H. Gielen, David T.W. Jones, Dominik Sturm, Stefan M. Pfister, Nicolas U. Gerber, Michael A. Grotzer, Elke Pfaff, André O. von Bueren, Darren Hargrave, Guirish A. Solanki, Filip Jadrijevic Cvrlje, Gertjan J.L. Kaspers, William P. Vandertop, Jacques Grill, Simon Bailey, Veronica Biassoni, Maura Massimino, Raphaël Calmon, Esther Sanchez, Brigitte Bison, Monika Warmuth-Metz, James Leach, Blaise Jones, Dannis G. van Vuurden, Christof M. Kramm, and Maryam Fouladi

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on May 10, 2018.

L.M.H., S.E.M.V.v.Z., C.M.K., and M.F. contributed equally to this work.

Corresponding author: Maryam Fouladi, MD, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH 45229; e-mail: maryam.fouladi@cchmc.org.

© 2018 by American Society of Clinical Oncology

0732-183X/18/3619w-1963w/\$20.00

ASSOCIATED CONTENT



Appendix
DOI: <https://doi.org/10.1200/JCO.2017.75.9308>



Data Supplement
DOI: <https://doi.org/10.1200/JCO.2017.75.9308>

DOI: <https://doi.org/10.1200/JCO.2017.75.9308>

ABSTRACT

Purpose

Diffuse intrinsic pontine glioma (DIPG) is a brainstem malignancy with a median survival of < 1 year. The International and European Society for Pediatric Oncology DIPG Registries collaborated to compare clinical, radiologic, and histomolecular characteristics between short-term survivors (STSs) and long-term survivors (LTSs).

Materials and Methods

Data abstracted from registry databases included patients from North America, Australia, Germany, Austria, Switzerland, the Netherlands, Italy, France, the United Kingdom, and Croatia.

Results

Among 1,130 pediatric and young adults with radiographically confirmed DIPG, 122 (11%) were excluded. Of the 1,008 remaining patients, 101 (10%) were LTSs (survival \geq 2 years). Median survival time was 11 months (interquartile range, 7.5 to 16 months), and 1-, 2-, 3-, 4-, and 5-year survival rates were 42.3% (95% CI, 38.1% to 44.1%), 9.6% (95% CI, 7.8% to 11.3%), 4.3% (95% CI, 3.2% to 5.8%), 3.2% (95% CI, 2.4% to 4.6%), and 2.2% (95% CI, 1.4% to 3.4%), respectively. LTSs, compared with STSs, more commonly presented at age < 3 or > 10 years (11% v 3% and 33% v 23%, respectively; $P < .001$) and with longer symptom duration ($P < .001$). STSs, compared with LTSs, more commonly presented with cranial nerve palsy (83% v 73%, respectively; $P = .008$), ring enhancement (38% v 23%, respectively; $P = .007$), necrosis (42% v 26%, respectively; $P = .009$), and extrapontine extension (92% v 86%, respectively; $P = .04$). LTSs more commonly received systemic therapy at diagnosis (88% v 75% for STSs; $P = .005$). Biopsies and autopsies were performed in 299 patients (30%) and 77 patients (10%), respectively; 181 tumors (48%) were molecularly characterized. LTSs were more likely to harbor a *HIST1H3B* mutation (odds ratio, 1.28; 95% CI, 1.1 to 1.5; $P = .002$).

Conclusion

We report clinical, radiologic, and molecular factors that correlate with survival in children and young adults with DIPG, which are important for risk stratification in future clinical trials.

J Clin Oncol 36:1963-1972. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Diffuse intrinsic pontine glioma (DIPG) is a malignant brainstem tumor of childhood for which median survival is < 1 year.¹ Long-term survival, historically defined as overall survival (OS) > 2 years, is reported in < 10% of patients.¹ Characteristics associated with longer survival include younger age, longer symptom latency, and absent ring enhancement on diagnostic magnetic resonance imaging.^{1,2} Up to 90% of DIPGs harbor a pathognomonic point mutation in *H3F3A* (65% of tumors) or *HIST1H3B* (25% of tumors); the latter seems to confer longer survival. Ten percent of patients have a histone 3 wild-type tumor.³

Involved-field radiation therapy (RT) remains standard of care but confers only a 3- to 4-month survival advantage. Benefit from neoadjuvant⁴ or adjuvant^{2,5} chemotherapy has not been consistently confirmed in prospective trials.

The rarity and inconsistent classification of DIPG, an imaging-based diagnosis, have long hampered cross-cohort comparisons. The primary aim of this multinational collaboration between the International DIPG Registry (IDIPGR) and European Society for Pediatric Oncology DIPG Registry (SIOPE-DIPGR)^{6,7} was to define clinical, radiologic, histologic, and molecular factors associated with short- and long-term survival in the largest cohort of centrally reviewed DIPGs to date.

MATERIALS AND METHODS

Study Population

The study was approved by the institutional review board at Cincinnati Children's Hospital Medical Center and included 1,130 patients with radiographically confirmed DIPG diagnosed from 1990 to 2015. IDIPGR patients (n = 409) were age 0 to 27 years from the United States, Canada, and Australia. SIOPE-DIPGR patients (n = 721) were age 0 to 21 years from the Netherlands, Germany, Austria, Switzerland, Italy, France, the United Kingdom, and Croatia. Patients were referred to the registries as previously described.^{6,7} Exclusion criteria are listed in Figure 1. No patients with neurofibromatosis type 1 were included.

Clinical Variables

Clinical data were abstracted (J.B., B.C., S.E.M.V.v.Z., and N.C.) using standardized case report forms. Cerebellar signs included dysmetria, ataxia, dysarthria, or nystagmus. Pyramidal tract signs included mono-, hemi-, or quadriplegia; hyperreflexia; or positive Babinski sign. Because overall survival (OS), defined as the time from diagnosis to death or last follow-up, is regarded as the most reliable outcome variable for DIPG, progression-free survival (PFS) was not reported. Short-term survivors (STSs), long-term survivors (LTSs), and very long-term survivors (VLTs) had OS times of < 24, ≥ 24, and ≥ 60 months, respectively. Two LTSs (patients DIPG-0016 and DIPG-0081) lost to follow-up at our data cutoff (January 1, 2017) were included in primary statistical analyses.

Radiologic Variables

Anonymized diagnostic magnetic resonance imaging was centrally reviewed (M.W., B.B., E.S., R.C., J.L., and B.J.) and classified as typical or unlikely DIPG; the latter were excluded. Typical DIPGs arose from and diffusely involved ≥ 50% of the pons. Exclusionary features included focally exophytic morphology, marked diffusion restriction, or secondary brainstem involvement by a tumor centered elsewhere in the brain or spine. Diagnostic imaging from all LTSs and 10% of STSs was cross-validated by

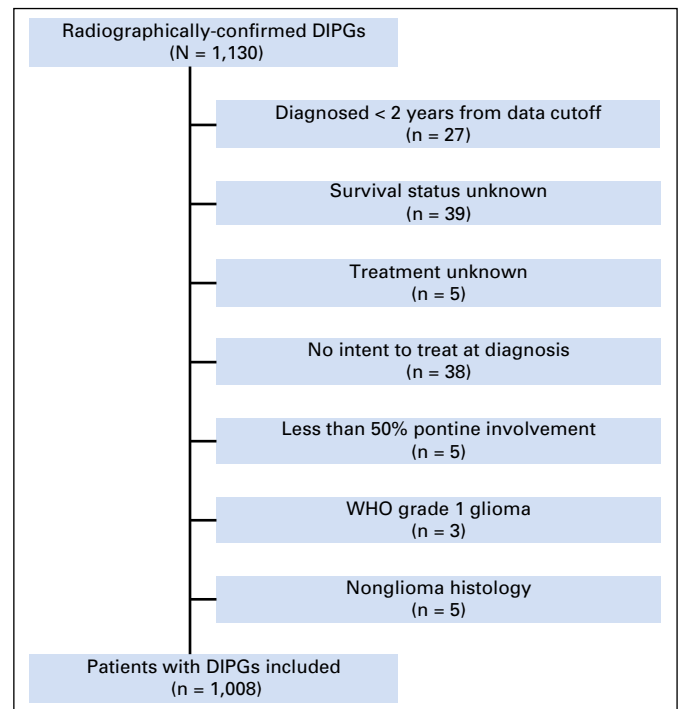


Fig 1. Flowchart of patients excluded from this study. DIPG, diffuse intrinsic pontine glioma.

a neuroradiologist from the other registry. Metastatic disease, defined as noncontiguous tumor in the brain or spine, was reported by individual sites but not centrally reviewed.

Histopathologic and Molecular Variables

Histology was defined according to 2007 WHO criteria⁸; based on availability of tissue in the registries, 61 tumor specimens were centrally reviewed (C.F. and C.H.). Databases were queried for common genomic alterations in DIPG. Histone mutations were assessed by Sanger sequencing, whole-exome sequencing, or whole-genome sequencing, polymerase chain reaction, or immunohistochemistry to detect H3K27M-mutant protein or H3K27 trimethylation (H3K27me3). Mutations in *H3F3A* (H3.3 K27M) or *HIST1H3B* (H3.1 K27M) were considered mutually exclusive even if both were not evaluated.

Statistical Analyses

Patient characteristics were summarized using medians and ranges or frequencies and percentages. Univariable analyses were performed using the Fisher's exact test or Wilcoxon rank sum test. Multivariable logistic regression was performed on variables with < 15% missing data and univariable $P < .1$; however, transverse tumor dimension was excluded as a result of high correlation with craniocaudal dimension. For subgroup analyses, multivariable logistic regression models were used to determine subgroup significance and adjusted for confounding factors. Survival was estimated using the Kaplan-Meier method. Statistical evaluation was performed using R (Version 3.1.3). $P < .05$ was considered significant.

RESULTS

Survival

A total of 1,008 patients met inclusion criteria (IDIPGR, n = 374; SIOPE-DIPGR, n = 634). Median survival time was 11 months

(interquartile range, 7.5 to 16 months), and 1-, 2-, 3-, 4-, and 5-year OS rates were 42.3% (95% CI, 38.1% to 44.1%), 9.6% (95% CI, 7.8% to 11.3%), 4.3% (95% CI, 3.2% to 5.8%), 3.2% (95% CI, 2.4% to 4.6%), and 2.2% (95% CI, 1.4% to 3.4%), respectively. Characteristics of 101 LTSs (10%) and 16 VLTs (1.6%) are shown in Figure 2 and Appendix Figure A1 (online only), respectively. Kaplan-Meier survival analyses for age, symptom duration, systemic therapy, histology, and molecular status are shown in Figure 3.

Clinical Presentation

Median age was 6.8 years (range, 0 to 26.8 years); 4% of patients were age < 3 years at diagnosis. Of patients with available data, 755 (82%) of 917, 468 (51%) of 915, and 567 (62%) of 920 patients presented with one or more cranial nerve (CN) palsy, pyramidal tract, or cerebellar sign, respectively. On univariable analysis (Table 1), LTSs were more likely to be age < 3 years (28% v 3% of STSs) or > 10 years (33% v 23% of STSs; $P < .001$) and had longer symptom duration at diagnosis. LTSs were less likely to present with CN palsy (72% v 83% of STSs; $P = .008$). Multivariable analyses (Table 2) confirmed association of age and symptom duration with long-term survival but failed to associate CN palsy with short-term survival.

Therapy

Thirty-eight patients (3%) who did not receive therapy at diagnosis (Appendix Fig A2A, online only) were excluded. Untreated patients were more often < 3 years old at diagnosis. Eleven patients underwent biopsy or autopsy. At progression, one patient received chemotherapy; no patients received RT. Median OS of untreated patients was 1 month (range, 0 to 135 months). Two patients were LTSs (both infants), including one who was alive 135 months after diagnosis (Appendix Fig A2B, online only).

The status of RT and systemic therapy was known for 968 patients; 721 patients (74%) received both RT and systemic therapy, 231 patients (24%) received RT alone, and 16 patients (2%) received systemic therapy alone. In univariable and multivariable analyses, LTSs more commonly received systemic therapy at diagnosis (88% v 75% for STSs; $P = .005$; odds ratio [OR], 3; 95% CI, 1.46 to 7.3; $P = .01$). Systemic therapy type was known for 702 patients (70%); 350 patients (50%) received cytotoxic therapy only, 193 patients (27%) received targeted therapy only, and 159 patients (23%) received both cytotoxic and targeted. On univariable analysis, type of targeted therapy yielded no survival difference (Table 1). However, multivariable logistic regression adjusted for age and symptom duration demonstrated greater odds of long-term survival with use of an epidermal growth factor receptor (EGFR) inhibitor (OR, 2.32; 95% CI, 1.1 to 4.82; $P = .03$) or bevacizumab (OR, 2.67; 95% CI, 1.09 to 6.55; $P = .03$), an anti-vascular endothelial growth factor (VEGF) antibody, at diagnosis (Table 2). Seventy-two patients (7%) underwent reirradiation at first or subsequent progression (as reported by individual sites). The rate of first progression recorded within 1 year of diagnosis was significantly lower in patients who underwent reirradiation compared with patients who did not (74% v 88%, respectively; $P = .007$).

Imaging

Table 1 lists diagnostic imaging characteristics. STSs demonstrated larger craniocaudal tumor dimension (43 v 40 mm for LTSs; $P = .04$) and higher rates of extrapontine extension (92% v

85% for LTSs; $P = .04$), tumor necrosis (45% v 26% for LTSs; $P = .009$), and ring enhancement (38% v 23% for LTSs; $P = .007$). Metastatic disease at diagnosis was reported in 18 STSs (2%) and no LTSs.

Histology and Molecular Characteristics

More SIOPE-DIPGR patients (39%) than IDIPGR patients (14%) underwent biopsy, and more IDIPGR patients (16%) than SIOPE-DIPGR patients (4%) underwent autopsy (Appendix Table A1, online only). LTSs from both registries were more often biopsied than STSs (38% v 28%, respectively; $P = .04$). Histology and WHO grade were known for 288 biopsy and 76 autopsy samples. WHO grade did not influence survival. Biopsy specimens included glioblastoma multiforme (GBM; $n = 80$), anaplastic astrocytoma ($n = 76$), anaplastic oligodendroglioma ($n = 10$), diffuse astrocytoma ($n = 37$), fibrillary astrocytoma ($n = 4$), oligodendroglioma ($n = 2$), low-grade astrocytoma ($n = 8$), and unknown ($n = 71$). Histology of autopsy tissue included GBM ($n = 48$), anaplastic astrocytoma ($n = 12$), diffuse astrocytoma ($n = 3$), and unknown ($n = 13$).

Of 376 patients from whom tissue was obtained, genomic data were available for 181 (48%) of patients (18% of the entire cohort; Data Supplement), including 21 LTSs (Fig 4). Global molecular assessment was undertaken for 44 patients (whole-genome sequencing, $n = 16$; whole-exome sequencing, $n = 25$; 450k methylation array, $n = 3$), whereas 98 patients underwent limited genomic sequencing (Sanger, $n = 80$; other targeted platform, $n = 18$), and 36 patients underwent immunohistochemistry alone. H3.1 K27M was associated with longer median OS (15 months) and long-term survival in multivariable analysis (OR, 1.28; 95% CI, 1.1 to 1.5; $P = .002$). In contrast, H3.3 K27M was associated with short-term survival (OR, 0.88; 95% CI, 0.78 to 0.99; $P = .04$; median survival, 10.4 months). Patients with H3 wild-type tumors ($n = 26$) had a median OS of 10.5 months. WHO grade did not correlate with histone mutation status. *TP53* and *ACVR1* mutations were not associated with survival. Of the 50 patients age > 10 years at diagnosis, who as a group demonstrated higher likelihood of long-term survival, 38 (78%) harbored H3.3 K27M, nine (18%) were H3 wild-type, and only three (6%) had H3.1 K27M.

DISCUSSION

This study confirms the relevance of some previously reported survival-associated factors in patients with DIPG and offers unique insight into 101 LTSs (including 16 VLTs). Median survival for all 1,008 patients was 11 months.^{1,5} Median survival times of LTSs and VLTs were 33 months (range, 24 to 156 months) and 78 months (range, 60 to 156 months), respectively. Of 16 surviving patients, two were lost to follow-up but were LTSs at the time of last contact (patients DIPG-0016 and DIPG-0081; OS, 33 and 36 months). The 2-year OS rate of 9.6% in this study was consistent with large retrospective studies^{2,5} that reported 9.2% and 9% 2-year OS rates in 153 and 316 patients with DIPG, respectively. The 1-year OS rate in our study (42.3%) is comparable to that reported by Hassan et al⁹ in a meta-analysis of 2,336 pediatric patients with high-grade brainstem glioma (41%); however, the 2- and 3-year OS rates of 15.3% (95% CI, 12% to 20%) and 7.3% (95% CI, 5.2% to 10%) in

Patient	Age (months)	Sex	CN Palsy	Cerebellar	Pyramidal	Symptom Duration (weeks)	Systemic Therapy	RT	Re-RT	Systemic Therapy Type	Tissue	WHO Grade	H3 Status	Status at LFU	OS (months)
DIPG 149	73	No	No	Yes	< 6	Yes	Yes	No	Other						24
DIPG 164	60	No	No	Yes	< 6	Yes	Yes	No	Other						24
DIPG 336	189	Yes	No	Yes	6-12	Yes	Yes	No							24
DIPG 354	125	Yes	No	Yes	< 6	Yes	Yes	No							24
FR 299	94	Yes	Yes	No	< 6	No	Yes	No					H3.3		24
GER 368	81	No	No	No	< 6	Yes	Yes	No	HDAC		4				24
GER 399	188	Yes	No	No	12-24	Yes	Yes	No							24
GOSH 30	49	Yes	No	Yes	< 6	Yes	Yes	No							24
NETH 162	204	Yes	Yes	Yes	6-12	Yes	Yes	No	EGFR		4	H3.3			24
DIPG 215	71	No	No	No	< 6	Yes	Yes	No	Unkn						24
DIPG 155	145	No	No	No	6-12	Yes	Yes	No			2				24
DIPG 22	93	No	No	Yes	< 6	Yes	Yes	No	Bev		4	H3.1			24
DIPG 83	97	Yes	No	Yes	< 6	Yes	Yes	No	Other						25
DIPG 160	54	Yes	Yes	Yes	< 6	Yes	Yes	No	Unkn						25
FR 333	70	No	Yes	No	< 6	Yes	Yes	Yes	EGFR		4	H3.1			25
GER 370	93	Yes	No	Yes	< 6	Yes	Yes	No	HDAC						25
IT 19	44	Yes	Yes	No	< 6	Yes	Yes	Yes	EGFR						25
IT 79	241	Yes	Yes	Yes	6-12	Yes	Yes	Yes	EGFR						25
NETH 111	97	No	No	Yes	< 6	No	Yes	No							25
DIPG 40	78	No	No	No	< 6	Yes	Yes	No	EGFR						25
DIPG 371	77	Yes	No	No	< 6	Yes	Yes	No	Other						26
FR 250	93	Yes	Yes	Yes	< 6	Yes	Yes	No							26
FR 258	75	No	No	Yes	< 6	Yes	Yes	No	EGFR			H3			26
FR 270	91	No	No	Yes	6-12	No	Yes	No							26
FR 337	39	Yes	Yes	Yes	< 6	Yes	Yes	Yes	EGFR		3	H3.1			26
GER 383	42	Yes	Yes	No	< 6	Yes	Yes	No	HDAC						26
DIPG 247	188	No	Yes	Yes	6-12	Yes	Yes	No							26
FR 350	79	Yes	No	Yes	< 6	Yes	Yes	Yes	mTOR		2	H3.3			27
GER 372	77	Yes	Yes	No	< 6	Yes	Yes	No							27
DIPG 35	145	Yes	No	Yes	< 6	Yes	Yes	No	Bev		3				27
DIPG 96	78	Yes	No	Yes	< 6	Yes	Yes	Yes							28
DIPG 526	98	Yes	Yes	No	6-12	Yes	Yes	No	Bev		2	H3.3			28
FR 366	170	Yes	No	Yes	< 6	Yes	Yes	No	EGFR			WT			28
GER 375	142	Yes	No	No	> 24	Yes	Yes	No			4	WT			28
GER 390	53	No	Yes	Yes	< 6	Yes	Yes	No							28
IT 10	64	Yes	No	Yes	< 6	Yes	Yes	No							28
GER 393	138	Yes	No	No	6-12	Yes	Yes	No							29
IT 11	48	Yes	Yes	Yes	< 6	Yes	Yes	No							29
GER 369	106	Yes	Yes	Yes	< 6	Yes	Yes	No	HDAC		2				30
GER 376	136	No	No	Yes	< 6	Yes	Yes	No	HDAC						30
GER 401	54	Yes	No	Yes	< 6	Yes	Yes	No							30
IT 20	207	Yes	No	No	< 6	Yes	Yes	Yes	EGFR		4				30
IT 81	104	Yes	No	No	12-24	Yes	Yes	Yes	EGFR						30
NETH 141	133	Yes	Yes	Yes	12-24	Yes	Yes	No							30
DIPG 157	56	Yes	Yes	Yes	12-24	Yes	Yes	No	EGFR			4			31
DIPG 79	33	Yes	Yes	Yes	6-12	Yes	Yes	No							32
GER 373	75	Yes	Yes	Yes	< 6	No	Yes	No							32
NETH 160	147	Yes	Yes	Yes	< 6	No	Yes	No							32
DIPG 107	54	Yes	Yes	Yes	< 6	Yes	Yes	No			2				32
DIPG 31	34	No	No	No	12-24	Yes	Yes	No			4	H3.3			32
DIPG 486	92	Yes	No	Yes	6-12	Yes	Yes	Yes	mTOR						33
GER 388	214	No	Yes	No	12-24	Yes	Yes	No			4	H3.3			33
DIPG 114	27	Yes	Yes	Yes	6-12	Yes	Yes	No							33
DIPG 16	264	No	No	Yes	6-12	Yes	Yes	No	Bev		2				34
CRO 6	49	Yes	Yes	No	12-24	Yes	Yes	No							34
FR 332	89	Yes	No	Yes	< 6	Yes	Yes	No	EGFR		4	H3.1			34
GER 371	97	Yes	No	No	< 6	Yes	Yes	No							34
DIPG 119	69	Yes	No	Yes	< 6	Yes	Yes	No				4	H3.1		35
GER 114	91	Yes	No	No	< 6	Yes	Yes	No							35
IT 17	202	Yes	Yes	Yes	> 24	Yes	Yes	Yes	EGFR						35
IT 13	86	Yes	Yes	No	6-12	Yes	Yes	No	EGFR						36
DIPG 81	321	No	No	No	6-12	Yes	Yes	No	EGFR		2				36
CRO 7	135	Yes	Yes	No	< 6	Yes	Yes	No			3				38
GER 379	39	No	No	No	< 6	Yes	Yes	No							39
DIPG 332	193	Yes	Yes	Yes	6-12	Yes	Yes	No	Other						39
FR 365	26	Yes	Yes	No	< 6	No	Yes	No				H3.3			40
IT 18	70	Yes	Yes	No	< 6	Yes	Yes	No	EGFR						40
NETH 184	109	No	Yes	Yes	12-24	No	Yes	No			4	H3.1			41
GER 374	41	Yes	No	Yes	< 6	Yes	Yes	No							42
GER 398	153	Yes	Yes	No	> 24	Yes	Yes	Yes			3	H3.1			45
DIPG 452	60	Yes	Yes	Yes	< 6	Yes	Yes	Yes	Unkn						46
GER 378	57	No	Yes	No	< 6	Yes	Yes	No			2				46
NETH 133	46	Yes	Yes	Yes	> 24	No	Yes	No			4				46
DIPG 68	153	No	No	No	6-12	Yes	Yes	No	Bev						49
GER 274	48	No	Yes	Yes	> 24	Yes	No	No			2	H3.3			49
GER 400	127	Yes	No	No	12-24	Yes	Yes	No	HDAC		2				49
GOSH 12	42	Yes	No	Yes	> 24	Yes	Yes	No							50
DIPG 251	80	No	No	Yes	< 6	No	Yes	No			3	H3.3			52
FR 302	24	Yes	No	No	< 6	Yes	Yes	Yes	EGFR		3	H3.3			52
DIPG 193	51	Yes	Yes	Yes	< 6	Yes	Yes	No							52
GER 392	42	Yes	Yes	No	> 24	Yes	Yes	No							53
NETH 112	27	Yes	No	No	6-12	No	Yes	No			2				54
NETH 98	50	Yes	Yes	Yes	> 24	No	Yes	No							56
DIPG 46	70	Yes	Yes	Yes	< 6	Yes	Yes	No							58
GER 385	149	No	No	No	> 24	Yes	Yes	No							59
GOSH 14	108	Yes	No	No	< 6	Yes	Yes	No							60
GER 380	161	Yes	No	No	> 24	Yes	Yes	No							67
GER 386	23	Yes	No	Yes	6-12	Yes	No	No							70
IT 15	33	Yes	Yes	No	12-24	Yes	Yes	No	EGFR						70
DIPG 449	169	Yes	Yes	Yes	> 24	Yes	Yes	No	Other						72
GER 387	169	No	No	No	6-12	Yes	Yes	Yes							75
NETH 120	134	No	Yes	Yes	< 6	No	Yes	No							75
NETH 194	26	No	Yes	Yes	> 24	Yes	Yes	No							77
DIPG 641	288	Yes	No	No	< 6	Yes	Yes	Yes	Bev		2	H3.3			78
GER 391	123	Yes	No	Yes	< 6	Yes	Yes	No							81
IT 14	107	Yes	No	No	12-24	Yes	Yes	No	EGFR						86
GER 397	23	Yes	Yes	No	< 6	Yes	Yes	Yes							89
GER 377	174	Yes	No	No	> 24	Yes	Yes	No	HDAC						99
DIPG 528	33	Yes	Yes	Yes	< 6	Yes	Yes	No	Other						101
UK 9	185	Yes	Yes	No	> 24	Yes	Yes	No	EGFR		2				102
IT 12	83	Yes	No	Yes	< 6	Yes	Yes	No							156
No Treatment at Diagnosis															
GER 382	37	Yes	No	No	< 6	No	No	No							56
NETH 164	28	Yes	Yes	Yes	> 24	No	No	No							135

Age
 < 3 years
 3-10 years
 > 10 years

Sex
 Female
 Male

CN, Cerebellar, Pyramidal
 Yes
 No

Symptom Duration
 < 6 weeks
 6-12 weeks
 12-24 weeks
 > 24 weeks

RT, Systemic Therapy, Re-RT
 Yes
 No

Systemic Therapy Type
 Cytotoxic
 Targeted
 Both

Tissue
 Biopsy
 Autopsy
 Both

WHO Grade
 2
 3
 4

Histone Status
 H3.3
 H3.1
 Wild-type

Status at LFU
 Alive
 Deceased

Survival
 < 2 years
 ≥ 2 years
 ≥ 3 years
 ≥ 4 years
 ≥ 5 years

Fig 2. Clinical, histologic, and molecular characteristics of long-term survivors of diffuse intrinsic pontine glioma. Bev, bevacizumab; CN, cranial nerve; CRO, Croatia; DIPG, International DIPG Registry; EGFR, epidermal growth factor receptor; FR, France; GER, Germany, Switzerland, Austria; GOSH, Great Ormond Street Hospital; HDAC, histone deacetylase inhibitor; IT, Italy; LFU, last follow-up; mTOR, mammalian target of rapamycin inhibitor; NETH, the Netherlands; OS, overall survival; Re-RT, reirradiation; RT, radiation therapy; UK, United Kingdom; Unkn, unknown.

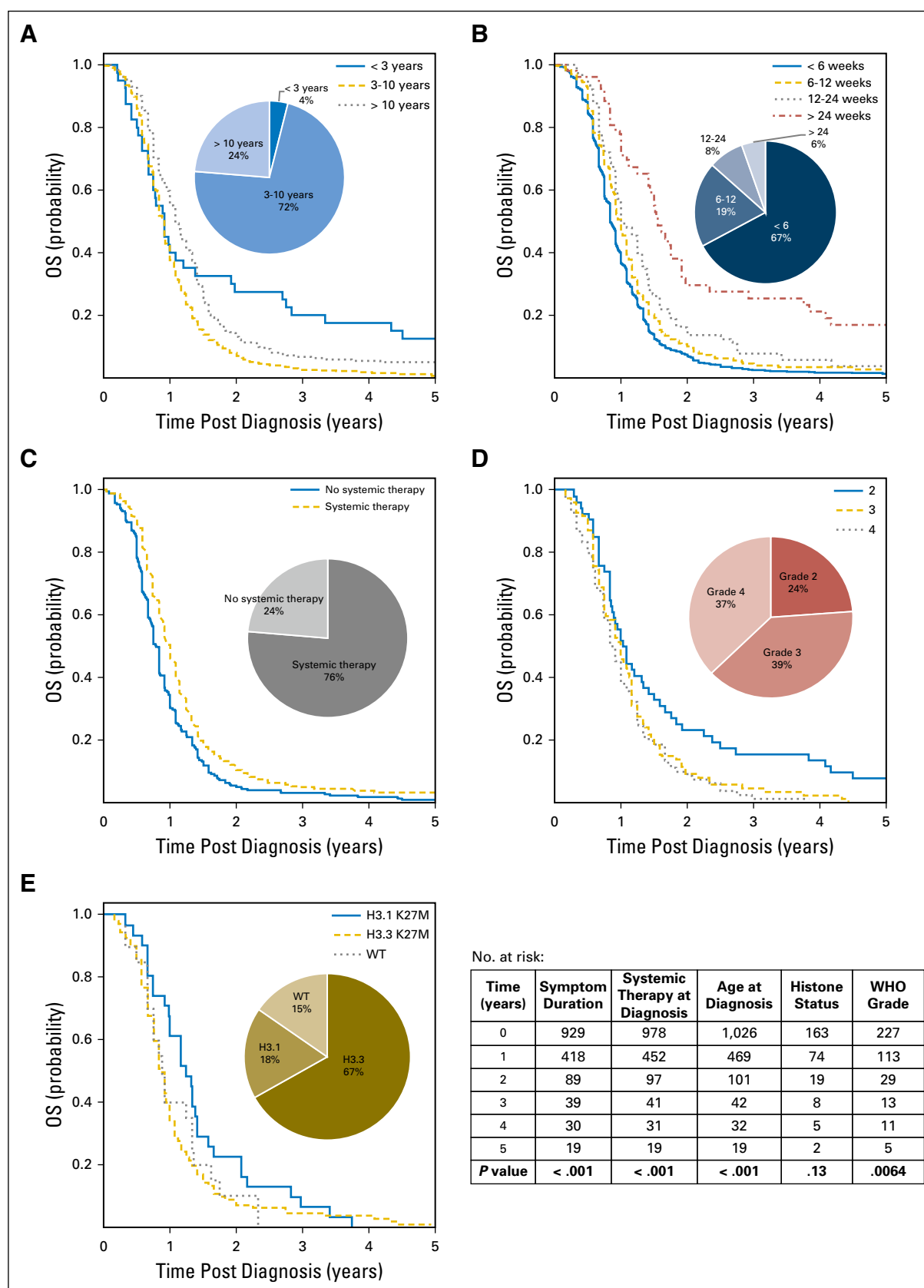


Fig 3. Kaplan-Meier curves representing overall survival (OS) based on (A) patient age (years), (B) symptom duration (weeks), (C) systemic therapy at diagnosis, (D) WHO grade, or (E) histone status. WT, wild type.

Table 1. Results of Univariable Analyses Comparing Clinical, Radiologic, and Histologic Characteristics of Long- and Short-Term Survivors of Diffuse Intrinsic Pontine Glioma

Characteristic	LTs (n = 101)	STs (n = 907)	P
Clinical			
Registry, No. (%)			.39
International	33 (9)	341 (91)	
SIOPE	68 (11)	566 (89)	
Sex, No. (%)			.46
Male	51 (50)	420 (46)	
Female	50 (50)	485 (54)	
Race, No. (%)			.43
African	4 (9)	43 (12)	
Asian	2 (4)	14 (4)	
White	36 (80)	237 (69)	
Other	3 (7)	50 (15)	
Median age, years (range)	7.2 (1.9-26.8)	6.8 (0-26.5)	.61
Age, years, No. (%)			< .001
< 3	11 (11)	29 (3)	
3-10	57 (56)	668 (74)	
> 10	33 (33)	205 (23)	
Symptom duration, weeks, No. (%)			< .001
< 6	45 (51)	564 (69)	
6-12	19 (21)	156 (19)	
12-24	11 (12)	62 (8)	
> 24	14 (16)	35 (4)	
Symptoms at diagnosis, No. (%)			.008
Cranial nerve palsy			
Yes	63 (73)	692 (83)	
No	25 (27)	137 (17)	
Pyramidal tract sign			.5
Yes	39 (44)	429 (52)	
No	50 (56)	397 (48)	
Cerebellar sign			.08
Yes	46 (53)	521 (63)	
No	41 (47)	312 (37)	
CSF diversion, No. (%)			1.00
Yes	22 (22)	196 (22)	
No	79 (78)	709 (78)	
Systemic therapy at diagnosis, No. (%)			.005
Yes	85 (88)	644 (75)	
No	12 (12)	214 (25)	
Category of systemic therapy, No. (%)			.07
Cytotoxic chemotherapy	36 (44)	314 (51)	
Targeted chemotherapy	19 (23)	174 (28)	
Both	27 (33)	132 (21)	
Chemotherapy type, No. (%)			.43
Cytotoxic	63 (56)	446 (60)	
EGFR inhibitor	21 (19)	114 (15)	.14
HDAC inhibitor	8 (7)	54 (7)	.68
mTOR inhibitor	2 (2)	14 (2)	1.00
Bevacizumab	8 (7)	44 (6)	.37
Other targeted agent	10 (9)	88 (12)	.74
Radiologic			
Median tumor size, mm (range)			
AP	36 (18-57)	36 (14-70)	.98
Transverse	43 (15-76)	45 (17-81)	.08
CC	40 (20-88)	43 (16-107)	.04
Median pons size, mm (range)			
AP	36 (21-50)	35 (20-58)	.12
Transverse	49 (31-62)	48 (22-78)	.62
Extrapontine extension, No. (%)			.04
Yes	78 (86)	739 (92)	
No	13 (14)	60 (8)	

(continued in next column)

Table 1. Results of Univariable Analyses Comparing Clinical, Radiologic, and Histologic Characteristics of Long- and Short-Term Survivors of Diffuse Intrinsic Pontine Glioma (continued)

Hemorrhage, No. (%)			.35
Yes	11 (14)	136 (19)	
No	68 (86)	588 (81)	
Necrosis, No. (%)			.009
Yes	20 (26)	306 (42)	
No	56 (74)	424 (58)	
Hydrocephalus, No. (%)			1.00
Yes	14 (18)	136 (18)	
No	65 (82)	632 (82)	
Tumor margin, No. (%)			.14
Ill defined	64 (75)	605 (82)	
Well defined	21 (25)	132 (18)	
Ring enhancement, No. (%)			.007
Yes	19 (23)	281 (38)	
No	63 (77)	457 (62)	
Histologic			
Biopsy, No. (%)			.03
Yes	38 (38)	249 (28)	
No	61 (62)	652 (72)	
Autopsy, No. (%)			.04
Yes	11 (18)	65 (10)	
No	49 (82)	597 (90)	
WHO grade, No. (%)			.08
2	12 (41)	40 (21)	
3	9 (31)	76 (40)	
4	8 (28)	73 (39)	

Abbreviations: AP, anterior-posterior; CC, craniocaudal; EGFR, epidermal growth factor receptor; HDAC, histone deacetylase; LTs, long-term survivors; mTOR, mammalian target of rapamycin; SIOPE, European Society for Pediatric Oncology; STs, short-term survivors.

their study were higher than those in our study (9.6% and 4.3%, respectively), likely reflecting the heterogeneity of their cohort, some whom may not have true DIPGs.

Previously, 43 VLTs had been reported in the literature.^{1,10-15} In Appendix Figure A1, we compare the characteristics of 22 previously published VLTs to our 16 VLTs, including eight (0.02% of the total cohort) who are alive with a median follow-up time of 6.5 years (range, 5 to 13 years). Our 5-year OS rate of 2.3% is comparable to the rate of 2.6% reported by Jackson et al¹ in 191 patients with DIPG; however, two of their five VLTs would have been excluded from our study for atypical magnetic resonance imaging features. Freeman et al¹² reported nine VLTs (6.9%) among 130 patients with DIPG treated with hyperfractionated RT (Pediatric Oncology Group 8495 trial), although only four of these patients (3%) would have met inclusion criteria in our study.

Age < 3 or > 10 years, longer symptom latency, lack of CN palsy, and systemic therapy at diagnosis were predictors of long-term survival. Of 41 patients age < 3 years at diagnosis, 36 received first-line RT with or without systemic therapy and five received systemic therapy alone. Although median OS for children age < 3 years (11 months) was the same as the entire cohort, a greater proportion was LTs or VLTs. Other studies have reported similar findings.^{1,2,5,16} Broniscer et al¹⁷ described 10 DIPG patients age < 3 years who received RT with or without chemotherapy (n = 8) or chemotherapy only (n = 2) at diagnosis (n = 6) or progression (n = 4). Five patients (50%) were LTs, including one treated without RT. Wagner et al⁵ similarly reported higher median survival in 13

Table 2. Results of Multivariable Cox Proportional Analysis of Clinical, Radiologic, and Molecular Variables Predicting Survival

Variable	Odds Ratio (95% CI)	P
Clinical		
Age, years		.02
< 3	2.82 (1.06 to 10.28)	
3-10	1.0	
> 10	2.24 (1.27 to 3.96)	
Symptom duration, weeks		< .001
< 6	1.0	
6-12	1.49 (0.76 to 2.92)	
12-24	2.43 (1.04 to 5.75)	
> 24	5.7 (2.77 to 14.54)	
Cranial nerve palsy		.08
Yes	0.57	
No	1.0	
Systemic therapy at diagnosis		.01
Yes	3 (1.46 to 7.3)	
No	1.0	
Category of systemic therapy		.14
Cytotoxic chemotherapy	1.0	
Targeted chemotherapy	1.03 (0.51 to 2.09)	
Both	1.84 (0.99 to 3.41)	
Systemic therapy type		
Cytotoxic	1.59 (0.73 to 3.45)	.24
EGFR inhibitor	2.32 (1.1 to 4.82)	.03
HDAC inhibitor	1.49 (0.62 to 3.6)	.38
mTOR inhibitor	0.98 (0.11 to 8.66)	.98
Bevacizumab	2.67 (1.09 to 6.55)	.03
Other targeted agent	0.71 (0.22 to 2.28)	.56
Radiologic		
Tumor dimension, mm		.58
AP	—	
Transverse	0.99 (0.96 to 1.02)	
CC	—	
Extrapontine extension		.91
Yes	0.95 (0.36 to 2.43)	
No	1.0	
Molecular		
H3F3A mutation		.04
Yes	1.0	
No	1.14 (1.01 to 1.28)	
HIST1H3B mutation		.002
Yes	1.0	
No	0.78 (0.67 to 0.91)	
ACVR1 mutation		.09
Yes	1	
No	0.75 (0.54 to 1.03)	
TP53 mutation		.36
Yes	1	
No	0.92 (0.76 to 1.1)	

NOTE. Necrosis, enhancement, and WHO grade were excluded because > 15% of data for these variables were missing. Types of systemic therapy are not mutually exclusive and were not excluded for multiple therapies.

Abbreviations: AP, anterior-posterior; CC, craniocaudal; EGFR, epidermal growth factor receptor; HDAC, histone deacetylase; mTOR, mammalian target of rapamycin.

children with DIPG age < 4 years compared with older children (13.6 v 10 months); only eight patients (61%) received RT. Although limitations to our data precluded making conclusions about biologic differences in this young age group, we postulate that unique mechanisms, such as potentially oncogenic *NTRK* fusions described in infantile midline high-grade gliomas,¹⁸ may underlie this observed survival advantage.

Patients age > 10 years at diagnosis had longer median OS (13 months) and were more likely to be LTSS. Bailey et al¹⁹ similarly reported five LTSS (all > 9 years old) among 43 patients with radiographically confirmed DIPG. In contrast, Veldhuijzen van Zanten et al¹⁶ reported no difference in OS between patients age 9 to 18 years versus younger patients. Although pathogenic mechanisms, such as low-grade histology or *IDH* mutation may influence survival in older patients, 78% of patients > 10 years old in our study harbored the poor prognostic H3.3 K27M mutation. Clinical and molecular characteristics for patients age > 18 years (n = 13) were also similar to their younger counterparts (Appendix Fig A3, online only).

Consistent with prior reports,^{1,2} the presence of symptoms for > 24 weeks at diagnosis was strongly associated with longer survival in univariable and multivariable analyses. CN palsy at diagnosis predicted shorter survival in univariable but not multivariable analysis. Previous studies reporting association of CN palsy with shorter survival included all brainstem tumors, not just DIPG, and/or diagnosis based on computed tomography scan, making comparison difficult.²⁰

Neoadjuvant or adjuvant systemic therapy correlated with long-term survival in both univariable and multivariable analyses. This finding differs from the long-standing view that systemic therapy provides no survival benefit for DIPG, a principle largely based on small, nonrandomized clinical trials. Effective cross-comparison of therapeutic studies for DIPG has been hindered by wide variation in inclusion criteria, as demonstrated in studies by Hargrave et al²¹ and Jansen et al²² in which only six of 29 DIPG-specific therapeutic trials between 1984 and 2012 had comparable eligibility. In a randomized trial, Wagner et al⁵ reported better median OS in patients with DIPG treated with adjuvant chemotherapy after RT (11.3 months) compared with patients treated with RT alone (9.5 months; *P* = .03). Similarly, others have reported superior median OS with use of adjuvant or neoadjuvant chemotherapy.⁴

Multivariable logistic regression demonstrated higher odds of long-term survival with use of EGFR inhibitors (eg, gefitinib, erlotinib, nimotuzumab, rindopepimut, cetuximab) or bevacizumab at diagnosis. A phase II study of gefitinib with RT in newly diagnosed patients with DIPG noted 2-year OS of 19.6% with PFS > 36 months in three patients.²³ In a biopsy-mandated phase I study of erlotinib with RT, EGFR overexpression trended toward longer PFS (10.1 months v 6.3 months in patients without EGFR overexpression; *P* = .058) but not OS.²⁴ Despite only modest activity of nimotuzumab in progressive DIPG, two patients lived for 663 and 481 days from the start of therapy.²⁵

Despite efficacy in adult GBM, bevacizumab has shown little activity in pediatric trials for newly diagnosed²⁶ or progressive DIPG²⁷ (median PFS, 2.3 months). However, in a phase I trial of vandetanib, a selective vascular endothelial growth factor receptor receptor 2 (VEGFR2) and EGFR inhibitor, in newly diagnosed DIPG, Broniscer et al²⁸ reported 2-year OS of 21.4%, and higher levels of plasma VEGF were associated with longer PFS (*P* = .02). Although numbers were too small to assess patient outcomes based on genomically matched targeted therapy, our findings support prospective assessment of biopsy tissue to define potential therapeutic targets, as recently undertaken in two multi-institution, multinational trials (ClinicalTrials.gov identifiers: NCT01182350 and NCT02233049).

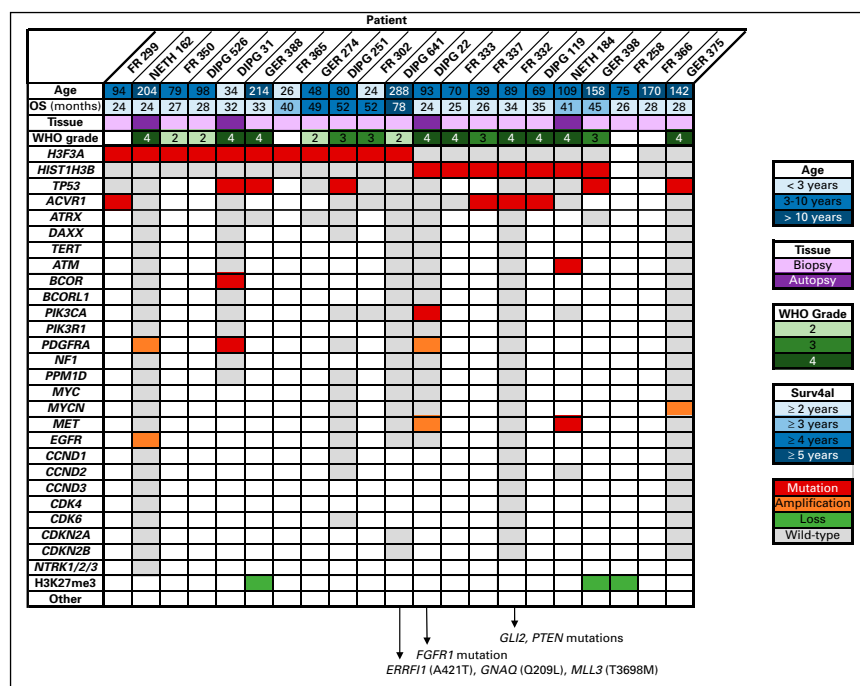


Fig 4. Genomic aberrations in long-term survivors of diffuse intrinsic pontine glioma (DIPG). DIPG, International DIPG Registry; FR, France; GER, Germany, Switzerland, Austria; NETH, the Netherlands; OS, overall survival.

Janssens et al²⁹ reported improved OS in 31 children with DIPG who received reirradiation at first progression (13.7 months) compared with a matched control cohort (10.3 months) despite similar PFS (8.2 v 7.7 months, respectively). Progression was not defined or centrally reviewed in our study; however, we noted that the proportion of patients with recorded progression within 1 year of diagnosis was significantly lower among patients who underwent reirradiation compared with those who did not, suggesting potential clinician bias to recommend reirradiation to patients with a more indolent disease course or potentially greater sensitivity to initial RT in patients who ultimately received reirradiation. As postulated by others,³⁰ increased RT sensitivity may be a manifestation of distinct biology. We did not report reirradiation-based outcomes given limitations conferred by analysis of registry data; more robust analysis of the effect of reirradiation in patients with DIPG would be best assessed prospectively in the context of a clinical trial.

On the basis of the radiographic definition of DIPG by Barkovich et al,³¹ patients with < 50% pontine involvement (n = 5) were excluded. Similar to a prior report,⁵ these patients had better median OS (20 months), and two patients were LTSs. Greater craniocaudal tumor dimension and extrapontine extension were associated with shorter survival; the former finding contrasts with a report by Poussaint et al,³² in which larger tumor at diagnosis was associated with longer survival.

As previously described,³² tumor necrosis and ring enhancement were associated with short-term survival in univariable analysis. Multivariable analysis was not performed because > 15% of data were missing for each variable, precluding comparison of our findings to the validated multiparametric prediction model published by Jansen et al.²

DIPG biology has been intensely studied since discovery of first-in-human histone mutations in 2012.¹⁵ Our findings confirm the independent association of H3.1 K27M and H3.3 K27M with long- and short-term survival, respectively.^{3,15} Median OS did not

significantly differ between histone wild-type and mutant DIPGs; this contrasts with the report by Khuong-Quang et al¹⁵ of longer median OS (4.59 years) for patients with histone wild-type tumors.

In univariable analysis, WHO grade did not differ between LTSs and STSs (Table 1), but on Kaplan-Meier analysis, WHO grade 2 was associated with longer survival (Fig 3D). In the most recent WHO classification of CNS tumors,³³ K27M-mutant midline gliomas are classified as WHO grade 4 regardless of histology, making this point less relevant. Tumors classified as primitive neuroectodermal tumors (now called embryonal tumor not otherwise specified) may represent true embryonal mimics of DIPG or result from sampling error in the context of intratumoral heterogeneity. Embryonal pontine tumors often demonstrate sharp margination and eccentric location, whereas others have radiologic characteristics indistinguishable from DIPG,³⁴ like those excluded from our study (Appendix Table A2, online only).

A limitation of this study is use of disease-specific registry data, which are susceptible to enrollment bias on the part of participating institutions (which tend to be large academic centers) and patients or families who self-refer. Variation in standards of care between countries and institutions may have also influenced findings. Anonymity of registry data makes some overlap of registry patients with those previously reported possible, biasing our findings toward similarity with published literature because they are not completely independent cohorts. The primary strength of this study is mandated central review of diagnostic imaging with cross-validation by highly experienced pediatric neuroradiologists and use of standardized case report forms. To our knowledge, this study represents the largest, most comprehensively annotated cohort of radiographically confirmed DIPGs reported, offering the most accurate rates of long- and very long-term survival for this rare tumor. Identification of robust survival-associated factors in this study is vital for development of prognostic subgroups and emphasizes patient subsets from whom the most could be learned from analyzing pretreatment biopsy

tissue. Understanding biologic differences that confer survival advantage in DIPG paves the road toward development of subgroup-specific therapies that, when implemented in the context of clinical trials, may improve outcomes for this devastating disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Lindsey M. Hoffman, Sophie E.M. Veldhuijzen van Zanten, Joshua Baugh, Adam Lane, James Leach, Dannis G. van Vuurden, Christof M. Kramm, Maryam Fouladi

Collection and assembly of data: Lindsey M. Hoffman, Sophie E.M. Veldhuijzen van Zanten, Niclas Colditz, Joshua Baugh, Brooklyn Chaney, Marion Hoffmann, Christine Fuller, Lili Miles, Cynthia Hawkins, Ute Bartels, Eric Bouffet, Stewart Goldman, Sarah Leary, Nicholas K. Foreman,

Roger Packer, Katherine E. Warren, Alberto Broniscer, Mark W. Kieran, Jane Minturn, Melanie Comito, Emmett Broxson, Chie-Schin Shih, Soumen Khatua, Murali Chintagumpala, Anne Sophie Carret, Nancy Yanez Escorza, Timothy Hassall, David S. Ziegler, Nicholas Gottardo, Hetal Dholaria, Renee Doughman, Martin Benesch, Rachid Drissi, Javad Nazarian, Nathalie Boddaert, Pascale Varlet, Géraldine Giraud, David Castel, Stephanie Puget, Chris Jones, Esther Hulleman, Piergiorgio Modena, Marzia Giagnacovo, Manila Antonelli, Torsten Pietsch, Gerrit H. Gielen, David T.W. Jones, Dominik Sturm, Stefan M. Pfister, Nicolas U. Gerber, Michael A. Grotzer, Elke Pfaff, André O. von Bueren, Darren Hargrave, Guirish A. Solanki, Filip Jadrijevic Cvrlje, Gertjan J.L. Kaspers, Jacques Grill, Simon Bailey, Veronica Biassoni, Maura Massimino, Raphaël Calmon, Brigitte Bison, Monika Warmuth-Metz, James Leach, Blaise Jones, Dannis G. van Vuurden, Christof M. Kramm, Maryam Fouladi

Data analysis and interpretation: Lindsey M. Hoffman, Sophie E.M. Veldhuijzen van Zanten, Joshua Baugh, Adam Lane, Christine Fuller, Lili Miles, Cynthia Hawkins, Nada Jabado, Esther Hulleman, Darren Hargrave, William P. Vandertop, Esther Sanchez, Brigitte Bison, Monika Warmuth-Metz, James Leach, Blaise Jones, Dannis G. van Vuurden, Christof M. Kramm, Maryam Fouladi

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

REFERENCES

- Jackson S, Patay Z, Howarth R, et al: Clinico-radiologic characteristics of long-term survivors of diffuse intrinsic pontine glioma. *J Neurooncol* 114: 339-344, 2013
- Jansen MH, Veldhuijzen van Zanten SE, Sanchez Aliaga E, et al: Survival prediction model of children with diffuse intrinsic pontine glioma based on clinical and radiological criteria. *Neuro Oncol* 17: 160-166, 2015
- Castel D, Philippe C, Calmon R, et al: Histone H3F3A and HIST1H3B K27M mutations define two subgroups of diffuse intrinsic pontine gliomas with different prognosis and phenotypes. *Acta Neuropathol* 130:815-827, 2015
- Gokce-Samar Z, Beuriat PA, Faure-Contier C, et al: Pre-radiation chemotherapy improves survival in pediatric diffuse intrinsic pontine gliomas. *Childs Nerv Syst* 32:1415-1423, 2016
- Wagner S, Warmuth-Metz M, Emser A, et al: Treatment options in childhood pontine gliomas. *J Neurooncol* 79:281-287, 2006
- Baugh J, Bartels U, Leach J, et al: The international diffuse intrinsic pontine glioma registry: An infrastructure to accelerate collaborative research for an orphan disease. *J Neurooncol* 132:323-331, 2017
- Veldhuijzen van Zanten SE, Baugh J, Chaney B, et al: Development of the SIOPE DIPG network, registry and imaging repository: A collaborative effort to optimize research into a rare and lethal disease. *J Neurooncol* 132:255-266, 2017
- Louis DN, Ohgaki H, Wiestler OD, et al: The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 114:97-109, 2007
- Hassan H, Pinches A, Picton SV, et al: Survival rates and prognostic predictors of high grade brain stem gliomas in childhood: A systematic review and meta-analysis. *J Neurooncol* 135:13-20, 2017
- Warren K, Bent R, Wolters PL, et al: A phase 2 study of pegylated interferon α -2b (PEG-Intron) in children with diffuse intrinsic pontine glioma. *Cancer* 118:3607-3613, 2012
- Hargrave D, Chuang N, Bouffet E: Conventional MRI cannot predict survival in childhood diffuse intrinsic pontine glioma. *J Neurooncol* 86:313-319, 2008
- Freeman CR, Bourgouin PM, Sanford RA, et al: Long term survivors of childhood brain stem gliomas treated with hyperfractionated radiotherapy: Clinical characteristics and treatment related toxicities. *Cancer* 77:555-562, 1996
- Allen J, Siffert J, Donahue B, et al: A phase I/II study of carboplatin combined with hyperfractionated radiotherapy for brainstem gliomas. *Cancer* 86:1064-1069, 1999
- Porkholm M, Valanne L, Lönnqvist T, et al: Radiation therapy and concurrent topotecan followed by maintenance triple anti-angiogenic therapy with thalidomide, etoposide, and celecoxib for pediatric diffuse intrinsic pontine glioma. *Pediatr Blood Cancer* 61:1603-1609, 2014
- Khuong-Quang D-A, Buczkowicz P, Rakopoulos P, et al: K27M mutation in histone H3.3 defines clinically and biologically distinct subgroups of pediatric diffuse intrinsic pontine gliomas. *Acta Neuropathol* 124: 439-447, 2012
- Veldhuijzen van Zanten SEM, Jansen MHA, Sanchez Aliaga E, et al: A twenty-year review of diagnosing and treating children with diffuse intrinsic pontine glioma in the Netherlands. *Expert Rev Anticancer Ther* 15:157-164, 2015
- Broniscer A, Laningham FH, Sanders RP, et al: Young age may predict a better outcome for children with diffuse pontine glioma. *Cancer* 113:566-572, 2008
- Wu G, Diaz AK, Paugh BS, et al: The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. *Nat Genet* 46: 444-450, 2014
- Bailey S, Howman A, Wheatley K, et al: Diffuse intrinsic pontine glioma treated with prolonged temozolomide and radiotherapy: Results of a United Kingdom phase II trial (CNS 2007 04). *Eur J Cancer* 49:3856-3862, 2013
- Fisher PG, Breiter SN, Carson BS, et al: A clinicopathologic reappraisal of brain stem tumor classification: Identification of pilocytic astrocytoma and fibrillary astrocytoma as distinct entities. *Cancer* 89:1569-1576, 2000
- Hargrave D, Bartels U, Bouffet E: Diffuse brainstem glioma in children: Critical review of clinical trials. *Lancet Oncol* 7:241-248, 2006
- Jansen MHA, van Vuurden DG, Vandertop WP, et al: Diffuse intrinsic pontine gliomas: A systematic update on clinical trials and biology. *Cancer Treat Rev* 38:27-35, 2012
- Pollack IF, Stewart CF, Kocak M, et al: A phase II study of gefitinib and irradiation in children with newly diagnosed brainstem gliomas: A report from the Pediatric Brain Tumor Consortium. *Neuro Oncol* 13:290-297, 2011
- Georger B, Hargrave D, Thomas F, et al: Innovative Therapies for Children with Cancer pediatric phase I study of erlotinib in brainstem glioma and relapsing/refractory brain tumors. *Neuro Oncol* 13: 109-118, 2011
- Bartels U, Wolff J, Gore L, et al: Phase 2 study of safety and efficacy of nimotuzumab in pediatric patients with progressive diffuse intrinsic pontine glioma. *Neuro Oncol* 16:1554-1559, 2014
- Hummel TR, Salloum R, Drissi R, et al: A pilot study of bevacizumab-based therapy in patients with newly diagnosed high-grade gliomas and diffuse intrinsic pontine gliomas. *J Neurooncol* 127:53-61, 2016
- Gururangan S, Fangusaro J, Poussaint TY, et al: Efficacy of bevacizumab plus irinotecan in children with recurrent low-grade gliomas: A Pediatric Brain Tumor Consortium study. *Neuro Oncol* 16:310-317, 2014
- Broniscer A, Baker JN, Tagen M, et al: Phase I study of vandetanib during and after radiotherapy in children with diffuse intrinsic pontine glioma. *J Clin Oncol* 28:4762-4768, 2010
- Janssens GO, Gandola L, Bolle S, et al: Survival benefit for patients with diffuse intrinsic pontine glioma (DIPG) undergoing re-irradiation at first progression: A matched-cohort analysis on behalf of the SIOPE-HGG/DIPG working group. *Eur J Cancer* 73: 38-47, 2017
- Morales La Madrid A, Santa-Maria V, Cruz Martinez O, et al: Second re-irradiation for DIPG

progression, re-considering “old strategies” with new approaches. *Childs Nerv Syst* 33:849-852, 2017

31. Barkovich AJ, Krischer J, Kun LE, et al: Brain stem gliomas: A classification system based on magnetic resonance imaging. *Pediatr Neurosurg* 16: 73-83, 1990-1991

32. Poussaint TY, Kocak M, Vajapeyam S, et al: MRI as a central component of clinical trials analysis in brainstem glioma: A report from the Pediatric Brain Tumor Consortium (PBTC). *Neuro Oncol* 13:417-427, 2011

33. David N, Louis MD, Ohgaki H: WHO Classification of Tumours of the Central Nervous System.

Geneva, Switzerland, World Health Organization, 2007

34. Sufit A, Donson AM, Birks DK, et al: Diffuse intrinsic pontine tumors: A study of primitive neuroectodermal tumors versus the more common diffuse intrinsic pontine gliomas. *J Neurosurg Pediatr* 10:81-88, 2012

Affiliations

Lindsey M. Hoffman and **Nicholas K. Foreman**, University of Colorado Denver; **Lindsey M. Hoffman** and **Nicholas K. Foreman**, Children's Hospital Colorado, Aurora, CO; **Sophie E.M. Veldhuijzen van Zanten**, **Esther Hulleman**, **Gertjan J.L. Kaspers**, **Esther Sanchez**, and **Dannis G. van Vuurden**, Vrije Universiteit University Medical Center, Amsterdam; **William P. Vandertop**, Academy of Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands; **Niclas Colditz**, **Marion Hoffmann**, **Brigitte Bison**, **Monika Warmuth-Metz**, and **Christof M. Kramm**, University Medical Center Goettingen, Goettingen; **Torsten Pietsch** and **Gerrit H. Gielen**, University of Bonn Medical Center, Bonn; **David T.W. Jones**, **Dominik Sturm**, **Stefan M. Pfister**, and **Elke Pfaff**, German Cancer Research Center, Hopp-Children's Cancer Center at the Nationale Centrum für Tumorerkrankungen Heidelberg, and German Consortium for Translational Cancer Research; **Dominik Sturm**, **Stefan M. Pfister**, and **Elke Pfaff**, Heidelberg University Hospital, Heidelberg, Germany; **Joshua Baugh**, **Brooklyn Chaney**, **Adam Lane**, **Christine Fuller**, **Nancy Yanez Escorza**, **Renee Doughman**, **Rachid Drissi**, **James Leach**, **Blaise Jones**, and **Maryam Fouladi**, Cincinnati Children's Hospital Medical Center, Cincinnati; **Emmett Broxson**, Wright State University and The Children's Medical Center, Dayton, OH; **Lili Miles**, Nemours Children's Hospital, Orlando, FL; **Cynthia Hawkins**, **Ute Bartels**, and **Eric Bouffet**, The Hospital for Sick Children, Toronto, Ontario; **Anne Sophie Carret**, Centre Hospitalier Universitaire Sainte-Justine; **Nada Jabado**, McGill University, Montreal, Quebec, Canada; **Stewart Goldman**, Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, IL; **Sarah Leary**, Seattle Children's Hospital, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA; **Roger Packer**, Children's National Health System; **Javad Nazarian**, Children's National Medical Center, Washington, DC; **Katherine E. Warren**, National Cancer Institute, Bethesda, MD; **Alberto Broniscer**, St Jude Children's Research Hospital, Memphis, TN; **Mark W. Kieran**, Dana-Farber Boston Children's Cancer and Blood Disorders Center, Boston, MA; **Jane Minturn**, Children's Hospital of Philadelphia and The Perelman School of Medicine at the University of Pennsylvania, Philadelphia; **Melanie Comito**, The Pennsylvania State University, Hershey, PA; **Chie-Schin Shih**, Indiana University, Indianapolis, IN; **Soumen Khatua**, The University of Texas MD Anderson Cancer Center; **Murali Chintagumpala**, Texas Children's Cancer and Hematology Centers, Baylor College of Medicine, Houston, TX; **Timothy Hassall**, Lady Cilento Children's Hospital, Brisbane, Queensland; **David S. Ziegler**, Kids Cancer Centre, Sydney Children's Hospital, Randwick; **David S. Ziegler**, University of New South Wales, Sydney, New South Wales; **Nicholas Gottardo** and **Hetal Dholaria**, Princess Margaret Hospital for Children, Perth, Western Australia, Australia; **Martin Benesch**, Medical University of Graz, Graz, Austria; **Nathalie Boddaert**, **Stephanie Puget**, and **Raphaël Calmon**, Hôpital Necker Enfants Malades; **Pascale Varlet**, Hôpital Sainte-Anne, Université Paris V Descartes, Sorbonne Paris Cité, Paris; **Géraldine Giraud**, **David Castel**, and **Jacques Grill**, Gustave Roussy, Université Paris-Sud, Université Paris-Saclay, Villejuif, France; **Géraldine Giraud**, Uppsala University, Uppsala, Sweden; **Chris Jones**, The Institute of Cancer Research, Sutton; **Darren Hargrave**, Great Ormond Street Hospital, London; **Guirish A. Solanki**, Birmingham Women's and Children's Hospital, Birmingham; **Simon Bailey**, Great North Children's Hospital, Victoria Wing, Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom; **Piergiorgio Modena** and **Marzia Giagnacovo**, Sant' Anna Como General Hospital, Como; **Manila Antonelli**, Sapienza University of Rome, Rome; **Veronica Biassoni** and **Maura Massimino**, Fondazione Istituto Di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori, Milan, Italy; **Nicolas U. Gerber** and **Michael A. Grotzer**, University Children's Hospital of Zurich, Zurich; **André O. von Bueren**, University Hospital of Geneva and University of Geneva, Geneva, Switzerland; and **Filip Jadrjevic Cvrlje** and **Gertjan J.L. Kaspers**, Children's Hospital Zagreb, Zagreb, Croatia.

Support

Supported by the Diffuse Intrinsic Pontine Glioma (DIPG) Collaborative, The Cure Starts Now Foundation, Hope for Caroline Foundation, Julian Boivin Courage for Cures Foundation, Abbie's Army, Michael Mosier Defeat DIPG Foundation, Reflections of Grace Foundation, The Cure Starts Now Australia, Brooke Healey Foundation, Soar With Grace Foundation, Jeffrey Thomas Hayden Foundation, Cure Brain Cancer Foundation, The Jones Family Foundation, Musella Foundation, Pray, Hope Believe Foundation, Smiles for Sophie Foundation, Benny's World, Love Chloe Foundation, Aiden's Avengers, A Cure from Caleb Society, The Operation Grace White Foundation, Ryan's Hope, Wayland Villars DIPG Foundation, American Childhood Cancer Organization, Juliana Rose Donnelly Trust, Sheila Jones and Friends, The Ellie Kavalieros DIPG Research Fund, Voices Against Brain Cancer, Semmy Foundation (S.E.M.V.v.Z. and E.H.). Also supported by the Associazione Bianca Garavaglia Onlus, Il fondo di Giò (M.M. and V.B.), Vrije Universiteit Medical Center CCA Children (D.G.v.V.), and the Deutsche Kinderkrebsstiftung (C.M.K., M.H., N.C., and A.O.v.B.). German patient data were obtained by funding of the Deutsche Kinderkrebsstiftung.



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Clinical, Radiologic, Pathologic, and Molecular Characteristics of Long-Term Survivors of Diffuse Intrinsic Pontine Glioma (DIPG): A Collaborative Report From the International and European Society for Pediatric Oncology DIPG Registries

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Lindsey M. Hoffman

No relationship to disclose

Sophie E.M. Veldhuijzen van Zanten

No relationship to disclose

Niclas Colditz

No relationship to disclose

Joshua Baugh

No relationship to disclose

Brooklyn Chaney

No relationship to disclose

Marion Hoffmann

No relationship to disclose

Adam Lane

No relationship to disclose

Christine Fuller

No relationship to disclose

Lili Miles

Honoraria: Aviana

Cynthia Hawkins

Research Funding: Bayer

Patents, Royalties, Other Intellectual Property: RDLP 1001: Methods and application of low-grade glioma-specific genetic panel and analysis for clinical diagnostic and prognostic use; operationalized and implemented ependymoma CpG methylator phenotype (CIMP) subgrouping test in clinical setting; operationalized and implemented medulloblastoma subgroup test in clinical setting; GDF-15 as a prognostic biomarker for NK cell therapy; methods and application of sarcoma-specific genetic panel analysis for clinical diagnostic and prognostic use

Ute Bartels

No relationship to disclose

Eric Bouffet

Research Funding: Bristol-Myers Squibb (Inst), Roche (Inst)

Stewart Goldman

Consulting or Advisory Role: Novartis

Travel, Accommodations, Expenses: Novartis

Sarah Leary

No relationship to disclose

Nicholas K. Foreman

No relationship to disclose

Roger Packer

No relationship to disclose

Katherine E. Warren

No relationship to disclose

Alberto Broniscer

No relationship to disclose

Mark W. Kieran

Consulting or Advisory Role: Novartis, Bayer, Boehringer Ingelheim, Sigma Tau, Merck, Bristol-Myers Squibb, Takeda

Speakers' Bureau: Merck Sharp & Dohme

Travel, Accommodations, Expenses: Merck Sharp & Dohme

Jane Minturn

No relationship to disclose

Melanie Comito

No relationship to disclose

Emmett Broxson

No relationship to disclose

Chie-Schin Shih

Travel, Accommodations, Expenses: Exelixis

Soumen Khatua

No relationship to disclose

Murali Chintagumpala

No relationship to disclose

Anne Sophie Carret

Employment: Seattle Genetics

Nancy Yanez Escorza

No relationship to disclose

Timothy Hassall

No relationship to disclose

David S. Ziegler

No relationship to disclose

Nicholas Gottardo

No relationship to disclose

Hetal Dholaria

No relationship to disclose

Renee Doughman

No relationship to disclose

Martin Benesch

No relationship to disclose

Rachid Drissi

Research Funding: PTC Therapeutics

Javad Nazarian

No relationship to disclose

Nada Jabado

No relationship to disclose

Nathalie Boddaert

No relationship to disclose

Pascale Varlet

Research Funding: Novartis (Inst), Boehringer Ingelheim (Inst), Roche (Inst)

Géraldine Giraud

No relationship to disclose

David Castel

No relationship to disclose

Stephanie Puget

No relationship to disclose

Chris Jones

Consulting or Advisory Role: Roche

Research Funding: Roche

Travel, Accommodations, Expenses: Roche

Esther Hulleman

No relationship to disclose

Piergiorgio Modena

No relationship to disclose

Marzia Giagnacovo

No relationship to disclose

Manila Antonelli

No relationship to disclose

Torsten Pietsch

Honoraria: Chugai Pharma

Travel, Accommodations, Expenses: Chugai Pharma

Gerrit H. Gielen

No relationship to disclose

David T.W. Jones

Patents, Royalties, Other Intellectual Property: Patent: Mutations of histone proteins associated with proliferative disorders; patent pending: DNA methylation-based method for classifying tumor species

Dominik Sturm

No relationship to disclose

Stefan M. Pfister

No relationship to disclose

Nicolas U. Gerber

No relationship to disclose

Michael A. Grotzer

No relationship to disclose

Elke Pfaff

No relationship to disclose

André O. von Bueren

No relationship to disclose

Darren Hargrave

Consulting or Advisory Role: AstraZeneca, Genentech, Novartis, Bayer, Boehringer Ingelheim

Research Funding: AstraZeneca

Expert Testimony: AstraZeneca

Travel, Accommodations, Expenses: Boehringer Ingelheim, Novartis, Genentech

Other Relationship: Celgene, Novartis, Bristol-Myers Squibb, Epizyme, AbbVie

Guirish A. Solanki

Honoraria: Biomarin

Consulting or Advisory Role: Biomarin

Travel, Accommodations, Expenses: Biomarin

Filip Jadrijevic Cvrlje

No relationship to disclose

Gertjan J.L. Kaspers

No relationship to disclose

William P. Vandertop

No relationship to disclose

Jacques Grill

Research Funding: Roche, Novartis, Bristol-Myers Squibb

Simon Bailey

No relationship to disclose

Veronica Biassoni

No relationship to disclose

Maura Massimino

Consulting or Advisory Role: Genentech

Raphaël Calmon

No relationship to disclose

Esther Sanchez

No relationship to disclose

Brigitte Bison

No relationship to disclose

Monika Warmuth-Metz

No relationship to disclose

James Leach

No relationship to disclose

Blaise Jones

No relationship to disclose

Dannis G. van Vuurden

No relationship to disclose

Christof M. Kramm

No relationship to disclose

Maryam Fouladi

No relationship to disclose

Acknowledgment

We thank the children and families who have suffered from diffuse intrinsic pontine glioma (DIPG) for their invaluable contribution to this research. Special thanks also to KPMG for the pro bono support of this project and for validation of design and security of the European Society for Pediatric Oncology (SIOPE) DIPG Registry and Imaging Repository.

Appendix

Study	Patient	Age	Sex	CN Palsy	Cerebellar	Pyramidal	Symptom Duration (weeks)	Systemic Therapy	RT	Re-RT	Systemic Therapy Type	Tissue	WHO Grade	H3 Status	Status at LFU	OS (months)
IDIPG/SIOPE-DIPG Registries	GOSH 14	108	Yes	No	No	< 6	Yes	Yes	Yes							60
	GER 380	161	Yes	No	No	> 24	Yes	Yes	No							67
	GER 386	23	Yes	No	Yes	6-12	Yes	No	No							70
	IT 15	33	Yes	Yes	No	12-24	Yes	Yes	No	EGFR						70
	DIPG 449	169		No	No	> 24	Yes	Yes	No	Other						72
	GER 387	169	No	No	No	6-12	Yes	Yes	Yes							75
	NETH 120	134	No	Yes	Yes	< 6	No	Yes	No							75
	NETH 194	26	No	Yes	Yes	> 24	Yes	Yes	No							77
	DIPG 641	288	Yes	No	No	< 6	Yes	Yes	No	Bev		2	H3.3			78
	GER 391	123	Yes	No	Yes	< 6	Yes	Yes	No							81
	IT 14	101	Yes	No	No	12-24	Yes	Yes	No	EGFR						86
	GER 397	23	Yes	Yes	No	< 6	Yes	Yes	Yes							89
	GER 377	174	Yes	No	No	> 24	Yes	Yes	No	HDAC						99
	DIPG 528	33		< 6	Yes	Yes	No	Other								101
	UK 9	185	Yes	Yes	No	> 24	Yes	Yes	No	EGFR		2				102
	IT 12	83	Yes	No	Yes	< 6	Yes	Yes	No							156
Jackson et al ¹	SJCRH 5	197	Yes	Yes	Yes	< 6	Yes	Yes	EGFR							64
	SJCRH 3	88	Yes	Yes	Yes	> 24	Yes	Yes	EGFR							94
	SJCRH 4	101	Yes	Yes	Yes	< 6	Yes	Yes	Other							117
	SJCRH 1	13	Yes	Yes	Yes	> 24	Yes	Yes			2					120
	SJCRH 2	30	Yes	Yes	Yes	> 24	Yes	Yes								158
Freeman et al ¹²	POG 9	78	Yes	Yes	No	> 24	No	Yes								64
	POG 6	144	No	No	No	< 6	No	Yes				3				78
	POG 8	86	Yes	Yes	Yes	6-12	No	Yes								86
	POG 2	96	Yes	Yes	Yes	6-12	No	Yes				2				89
	POG 4	66	Yes	Yes	Yes	> 24	No	Yes				2				91
	POG 7	86	Yes	No	No	6-12	No	Yes								92
	POG 5	180	Yes	No	No	6-12	No	Yes				3				96
	POG 3	144	Yes	Yes	Yes	< 6	No	Yes								99
Khuong-Quang et al ¹⁵	POG 1	132	No	Yes	No	> 24	No	Yes				2				109
	Sick Kids 1	20										4	WT			75+
	Sick Kids 2	180										3	WT			190+
	Sick Kids 3	30										3	WT			158+
Porkholm et al ¹⁴	Sick Kids 4	36										4	WT			120+
	Finland 1	156										2/3				60+
Warren et al ¹⁰	NCI 1	31						Yes	Yes	No	Other					60+
Hargrave et al ¹¹	Toronto 1	4	Yes	No	No	< 6	Yes	No	No							183
	Toronto 2	42	Yes	No	No	< 6	Yes	Yes	No							233

Fig A1. Very long-term survivors of diffuse intrinsic pontine glioma in the current study compared with those described in the literature. Yellow highlight indicates atypical radiologic features that would have been excluded in the current study. Bev, bevacizumab; CN, cranial nerve; DIPG, diffuse intrinsic pontine glioma; EGFR, epidermal growth factor; GER, Germany, Switzerland, Austria; GOSH, Great Ormond Street Hospital; HDAC, histone deacetylase inhibitor; HGG, high-grade glioma; IDIPGR, International Diffuse Intrinsic Pontine Glioma Registry; IT, Italy; LFU, last follow-up; NCI, National Cancer Institute; NETH, the Netherlands; OS, overall survival; POG, Pediatric Oncology Group; Re-RT, reirradiation; RT, radiation therapy; SIOPE, European Society for Pediatric Oncology; SJCRH, St Jude Children's Research Hospital; UK, United Kingdom; WT, wild type.

A

Clinical Variables	Untreated (n = 38)	Treated (n = 1,008)
LTS, No. (%)		
Yes	2 (5)	101 (10)
No	36 (95)	907 (90)
Age, years		
Median	6.3 (0-15.4)	6.8 (0-26.8)
< 3	10 (26%)	40 (4%)
≥ 3	28 (74%)	963 (96%)
Symptom duration, weeks		
< 6	26 (68%)	609 (67%)
6-12	8 (21%)	175 (19%)
12-24	1 (4%)	73 (8%)
> 24	3 (8%)	49 (6%)
Symptoms at diagnosis, No. (%)		
Cranial nerve palsy		
Yes	26 (79)	755 (82)
No	7 (21)	162 (18)
Pyramidal tract sign		
Yes	17 (52)	429 (52)
No	16 (48)	397 (48)
Cerebellar sign		
Yes	20 (62)	521 (63)
No	12 (38)	312 (37)
Median OS, months (range)	1 (0-135)	11 (0-167)

B

Patient	GER 382	NETH 164
Age (months)	37	28
Sex	Female	Male
CN palsy	Yes	Yes
Cerebellar	No	Yes
Pyramidal	No	Yes
Symptom duration (weeks)	< 6	> 24
Chemotherapy	No	No
RT	No	No
Re-RT	No	No
Status at LFU	Deceased	Alive
OS (months)	56	135

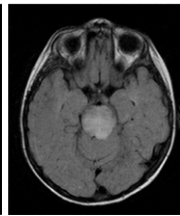
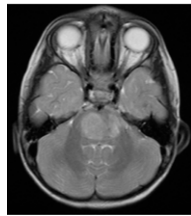


Fig A2. (A) Comparison of characteristics of patients who received therapy or did not receive therapy at diagnosis. (B) Magnetic resonance images and clinical characteristics of two long-term survivors (LTSs) of diffuse intrinsic pontine glioma who did not receive therapy. CN, cranial nerve; GER, Germany, Switzerland, Austria; LFU, last follow-up; NETH, the Netherlands; OS, overall survival; Re-RT, reirradiation; RT, radiation therapy.

Long-Term Survivors of Diffuse Intrinsic Pontine Glioma

Patient	Age	Sex	CN Palsy	Cerebellar	Pyramidal	Symptom Duration (weeks)	Chemotherapy	RT	Re-RT	Chemo Type	Tissue	WHO Grade	H3 Status	Status at LFU	OS (months)
DIPG 161	218		No	No	No	< 6	Yes	Yes	No	HDAC			H3.3		17
GER 346	223	Yes	Yes	Yes	6-12	Yes	Yes	No	HDAC		2	H3.3			13
DIPG 331	224	Yes	No	No	6-12	Yes	Yes	No	EGFR						18
DIPG 477	236	Yes	Yes	Yes	> 24	Yes	Yes	No							8
IT 79	241	Yes	Yes	Yes	6-12	Yes	Yes	Yes	EGFR						25
DIPG 7	246	No	No	No	6-12	Yes	Yes	No							11
DIPG18	257				6-12	Yes	Yes	No	Bev		3				14
DIPG 18	284	No	Yes	No	6-12	Yes	Yes	No	Bev		3	H3.3			69
DIPG 70	280	Yes	No	No	< 6	Yes	Yes	No	HDAC		3	H3.3			14
DIPG 641	288	Yes	No	No	< 6	Yes	Yes	Yes	Bev		2	H3.3			80
FR 343	302					Yes	Yes	No			3	H3.3			12
DIPG 23	318	No	No	Yes	< 6	Yes	Yes	No	Bev		4	WT			11
DIPG 81	321	No	No	No	6-12	Yes	Yes	No	Bev		2				7

Age

< 3 years

3-10 years

> 10 years

Sex

Female

Male

CN, Cerebellar, Pyramidal

Yes

No

Symptom Duration

< 6 weeks

6-12 weeks

12-24 weeks

> 24 weeks

RT, Chemo, Re-RT

Yes

No

Chemo Type

Cytotoxic

Targeted

Both

Tissue

Biopsy

Autopsy

WHO Grade

2

3

4

Histone Status

H3.3

H3 WT

Status at LFU

Alive

Deceased

Fig A3. Clinical, radiologic, and molecular characteristics of patients with diffuse intrinsic pontine glioma age > 18 years. Bev, bevacizumab; CN, cranial nerve; DIPG, International DIPG Registry; EGFR, epidermal growth factor; FR, France; GER, Germany, Switzerland, Austria; HDAC, histone deacetylase inhibitor; IT, Italy; LFU, last follow-up; OS, overall survival; Re-RT, reirradiation; RT, radiation therapy; WT, wild type.

Table A1. Biopsies and Autopsies Performed by Country or Region		
Country	No./Total No. (%)	
	Biopsy	Autopsy
SIOPE-DIPGR		
France	109/113 (96)	2/115 (2)
Germany/Switzerland/Austria	81/278 (29)	4/16 (25)
The Netherlands	29/114 (25)	10/113 (9)
Italy	17/79 (22)	0/71 (0)
Croatia	2/7 (29)	0/5 (0)
United Kingdom	7/43 (16)	0/43 (0)
IDIPGR		
United States/Canada/Australia	54/372 (15)	61/376 (16)

Abbreviations: IDIPGR: International Diffuse Intrinsic Pontine Glioma Registry; SIOPE-DIPGR, European Society for Pediatric Oncology Diffuse Intrinsic Pontine Glioma Registry.

Table A2. Clinical, Radiologic, and Molecular Characteristics of Patients With Primitive Neuroectodermal Tumor

Patient	Age (months)	Symptom Duration (weeks)	Symptoms	Treatment at Diagnosis	OS (months)	Source of Tissue	Molecular Findings
DIPG-0051	27	Unknown	Unknown	RT + vorinostat	6	Biopsy	WT H3.3
DIPG-0165	53	< 6	CN, pyramidal	RT + vorinostat	7	Biopsy	WT <i>PDGFRA</i> and <i>EGFR</i>
DIPG-0236	62	< 6	Unknown	RT	5	Autopsy	Mutant <i>TP53</i> and <i>NF1</i> Amplified <i>MYCN</i> WT H3.3, H3.1, <i>ACVR1</i> , <i>PDGFRA</i> , <i>EGFR</i> , <i>ATRX</i> , <i>DAXX</i> , <i>PIK3CA</i> , <i>MET</i> , <i>CDKN2A/B</i> , <i>CCND1/2</i> , <i>CDK6</i> , <i>PPM1D</i>

Abbreviations: CN, cranial nerve; DIPG, International DIPG Registry; OS, overall survival; RT, radiation therapy; WT, wild type.